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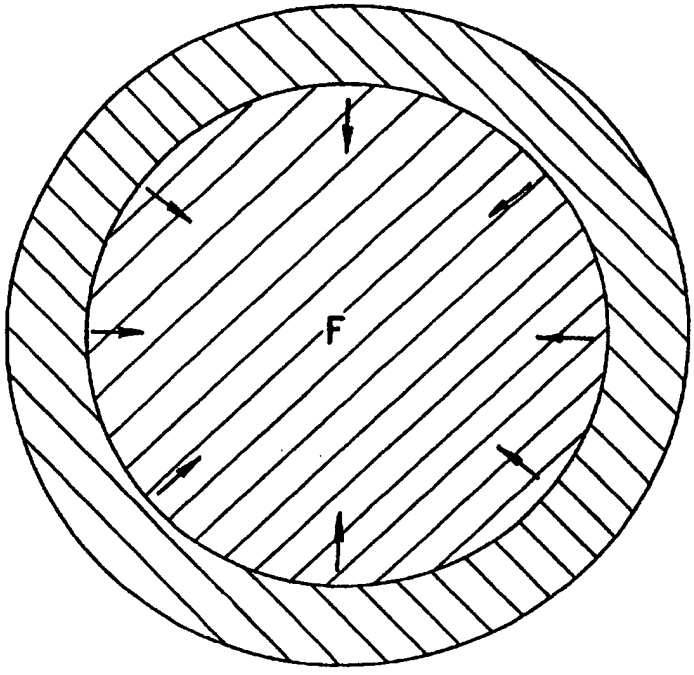
(57) Abstract

The present invention relates to methods of treating eustachian tube dysfunction using surfactants. In particular, it relates to the delivery of surfactants by inhalation to the eustachian tube to reduce its opening pressure. The surfactant compositions suitable for use in the invention are obtained from natural sources or produced synthetically. Bovine pulmonary surfactant is one example that is commercially available. The surfactant compositions are delivered by inhalation via the nasal and/or oral cavities as a liquid aerosol or in a dry powder formulation. A wide variety of uses is encompassed by the present invention including, but not limited to, the treatment of otologic disorders associated with eustachian tube dysfunction such as otitis media and dysfunction that results from acute changes in altitude.



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METHODS AND COMPOSITIONS F R TREATIN EUSTACHIAN TUBE DYSFUNCTION BY INHALATION

1. INTRODUCTI N

The present invention relates to the use of surfactant in the treatment of eustachian tube dysfunction. In particular, it relates to the delivery of surfactant by inhalation to the eustachian tube for the treatment of disorders associated with eustachian tube dysfunction such as otitis media with effusion.

2. BACKGROUND OF THE INVENTION

Otitis media (OM), inflammation of the middle ear, is a common disorder in children with 84% having one or more episodes by age three (Teele et al., 1989, *J. Infect. Dis.* 160:83-94). Frequently, such inflammation causes a collection of fluid, a condition known as otitis media with effusion (OME). In the United States, there are 9.3 million cases of acute OM each year in children under age two, and 1.9 million cases of persistent OME. Diagnosis and treatment of middle ear problems account for about 1/3 of all pediatric visits or approximately 30 million visits per year. For children under age fifteen, OM is the most frequently diagnosed middle ear disorder (80.5% of office visits). In 1990, an estimated 24.5 million office visits in the United States resulted in a principal diagnosis of OM. These accounted for 3.5% of all office visits. OM was the second most frequently documented diagnosis overall, after essential hypertension (Schappert, 1992, *Advance Data*, No. 214, Centers For Disease Control).

Estimates of the annual cost of treating OM medically and surgically approach 3 billion dollars (Berman, 1995, *New Engl. J. Med.* 332:1560-1565). Recently, aggressive efforts to standardize care of these patients with the goal of improving outcome and controlling cost have been instituted (Berman, 1995, *New Engl. J. Med.* 332:1560-1565; Kleinman et al., 1994, *JAMA* 271:1250-1255).

Eustachian tub dysfunction is associated with OM and/or OME. Structural factors affecting eustachian tube function in pediatric patients include short tube length, proximity of chronically infected adenoidal tissue and inefficient active tube opening by palatal musculature. While these are contributing factors in many pediatric patients, other factors that affect the population at large include mass lesions in the nasopharynx, iatrogenic injury to the eustachian tube orifice (Fornadley and Burns, 1994, *Otolaryngol. Head Neck* 110:110-114) and diseases that cause mucosal congestion and swelling such as infection and allergy. Biochemical changes are known to occur in the eustachian tube/middle ear system during inflammation. Grace et al. (1987, *Otolaryngol. Head Neck* 96:336-340) examined differences in phospholipid content between children and adults with middle ear effusions, and found that sphingomyelin was the major component of effusion fluid in adults. Phosphatidylcholine predominated in children. Svane-Knudsen et al. (1988, *Acta Otolaryngol.* 105:114-119) documented a reduction in the phosphatidylcholine/sphingomyelin ratio in children with secretory OM.

Efforts to improve eustachian tube function or bypass a poorly functioning eustachian tube include antimicrobial therapy, ventilation tube placement and adenoidectomy. These approaches focus on both the microbiologic and structural etiologies of poor eustachian tube function, especially in the pediatric patient. Failure to correct eustachian tube function and persistent OME result in hearing loss, delays in speech development and complications of chronic OM.

Flisberg et al. (1963, *Acta Otolaryngol.* 182:57-68) suggested that surfactants might be important in eustachian tube opening. Surface tension at an air-water interface is significantly reduced in the presence of these surface active substances, as shown in early pulmonary alveolar models (Avery and Mead, 1959, *Am. J. Dis. Child.* 97:517-523), and

more recently in the eustachian tube system (Hagan, 1977, *Laryngoscope* 87:1033-1045; Maves et al., 1981, *Otolaryngol. Head Neck* 89:307-316).

Surface tension in a sphere or tube lined with fluid favors collapse (Figure 1). The force needed to overcome this collapse is defined by the Law of LaPlace:

$F = T/R$

F = opening force (transluminal pressure)
T = surface tension (force per unit length)
R = radius (tube or sphere)

As T increases, the force required to open the tube increases. Applied to the eustachian tube, F corresponds to tubal opening pressure.

Two recent reports have shown that introduction of exogenous surfactants into the middle ear/eustachian tube system decreased opening force (pressure) (Fornadley and Burns, 1994, *Otolaryngol. Head Neck* 110:110-114; White, 1989, *Am. J. Otolaryngol.* 10:301-304). However, both studies utilized invasive methods for administering surfactants, which are not clinically practicable. For example, Fornadley and Burns administered surfactant via tympanotomy and middle ear irrigation after the animals were sacrificed. Similarly, White administered surfactant via a tube inserted through a hole drilled into the tympanic cavity.

It should be noted that while surfactant has been used to treat respiratory disorders, these conditions are distinct from eustachian tube dysfunction with respect to both their etiologies and clinical manifestations. Therefore, the therapeutic effects of surfactant in the lung in no way suggest that surfactant would be equally applicable to treating eustachian tube dysfunction.

Prior to the present invention, introduction of exogenous surfactants into the middle ear could only be accomplished invasively in patients having undergone or undergoing myringotomy and ventilation tube insertion. Since most patients with OME do not provide such access, such treatment has limited clinical application and is not presently a therapeutic option in the treatment of OME.

Therefore, there remains a n ed for a non-invasive method of delivering surfactants to the middle ear/eustachian tube system. Such a method is particularly desirable in the pediatric population in an effort to eliminate discomfort and morbidity associated with surgical access to middle ear.

3. SUMMARY OF THE INVENTION

The present invention relates to methods of treating eustachian tube dysfunction using a surfactant, and pharmaceutical compositions in which surfactant is the active therapeutic agent. In a particular embodiment, it relates to the delivery of a surfactant by inhalation to the eustachian tube for the treatment of otologic disorders, and pharmaceutical compositions of surfactant in a formulation that facilitates entry into the eustachian tube following inhalation via the nasal cavity or via a combination of the oral and nasal cavities.

The present invention is based, in part, on Applicant's discovery of a clinically practical, non-invasive and efficacious method of delivering a surfactant to the eustachian tube. As demonstrated in the example in Section 6, *infra*, inhaled nebulized surfactant is an efficacious therapeutic agent in reestablishing normal eustachian tube function by reducing its opening pressure. A wide variety of uses is encompassed by the present invention including, but not limited to, the treatment of various forms of eustachian tube dysfunction and its associated disorders such as acute and chronic OM, OME, barotitis media, acute mastoiditis, acute and chronic otomastoiditis, and tympanic membrane atelectasis as well as dysfunction resulting from acute changes in altitude. For the purpose of the present invention, the term "eustachian tube dysfunction" encompasses any clinical condition resulting from structural and/or physiological abnormalities of the eustachian tube, in which the common endpoint is reduced ventilation of the middle ear.

4. BRIEF DESCRIPTION F THE DRAWINGS

Figure 1. Surface tension at an air-liquid interface within a sphere or tube favors collapse.

Figure 2. Apparatus used to deliver nebulized surfactant to affected subjects.

Figure 3. Gradual pressurization of the middle ear system continues until the eustachian tube opens, denoted by a precipitous fall in system pressure.

Figure 4. Mean values of eustachian tube opening pressure for non-affected healthy ears and affected, surfactant-treated ears.

5. DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a clinically novel and practical method of delivering a surfactant to the eustachian tube of an individual. The invention further provides novel surfactant compositions suited for delivery to the eustachian tube via the nasal route by inhalation. In a specific embodiment illustrated by way of example in Section 6, *infra*, in a well-established animal model for OME (Daniel et al., 1982, *Ann. Otol.* 91:82-89), OME was induced in gerbils by transtympanic inoculation of heat-killed *Streptococcus pneumoniae*. This procedure is known to induce a serous effusion in the middle ears of gerbils that, in turn, increases eustachian tube opening pressure. The animals with microscopically confirmed OME were then treated with an inhaled nebulized surfactant for several days. When the eustachian tube opening pressure of both affected and non-affected animals was measured, there was no statistically significant difference. Mean opening pressure for ears without effusion (healthy ears) was 42.8 mmHg, and mean opening pressure for ears with effusion in animals treated with nebulized surfactant was 41.4 mmHg. Therefore, a

surfactant composition can be effectively delivered through inhalation to the eustachian tub to reduce its op ning pressure for the treatment of eustachian tube dysfunction and its associated disorders.

Although the specific procedures and methods described herein are exemplified using "SURVANTA" in a nebulizer, they are merely illustrative for the practice of the invention. Analogous compositions and procedures are equally applicable for human treatment.

5.1. SURFACTANT COMPOSITIONS

The present invention relates to a non-invasive method for delivering any surfactant composition to the eustachian tube. For the purpose of this invention, the term "surfactant" refers to any pharmaceutically acceptable surface active substance that reduces surface tension. Surfactant is generally composed of lipids and certain associated proteins. A well known example of such a substance is pulmonary surfactant produced by cells lining the pulmonary alveoli, preventing collapse during the respiratory cycle by reducing surface tension. Pulmonary surfactants have been produced artificially (United States Patent 4,312,860) and extracted from human or animal lung (EP 119056). One pharmaceutically acceptable natural animal pulmonary surfactant that has been used successfully to treat human respiratory disorders contains a high concentration of phospholipids (99%), a protein content of less than 1-1.5% and is devoid of free carbohydrates, cholesterol, triglycerides and cholesterol esters (United States Patent 5,024,995). This preparation was used therapeutically at about 200 mg of phospholipids/kg of body weight.

In a specific embodiment by way of example in Section 6, *infra*, "SURVANTA" (Ross Laboratories, Columbus, OH) was used to successfully treat animals with experimental OME. "SURVANTA" is a surfactant comprising a natural bovine lung extract that contains phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins to which colfosceril palmitate (dipalmitoylphosphatidylcholine),

palmitic acid, and tripalmitin are added to standardize the comp sition and to mimic surface-tension lowering properties of natural lung surfactant (United States Pat nt 5,013,720). The resulting composition provides 25 mg/ml phospholipids (including 11.0-15.5 mg/ml disaturated phosphatidylcholine), 0.5-1.75 mg/ml triglycerides, 1.4-3.5 mg/ml free fatty acids, and less than 1.0 mg/ml protein. It is suspended in 0.9% sodium chloride solution, heat-sterilized and it contains no preservatives. Its protein content consists of two hydrophobic, low molecular weight, surfactant-associated proteins commonly known as SP-B and SP-C (United States Patent 5,302,581). It does not contain the hydrophilic, large molecular weight surfactant-associated protein known as SP-A. Each ml of "SURVANTA" contains 25 mg of phospholipids.

Mammalian pulmonary surfactants suitable for use in the present invention include, but are not limited to, porcine, bovine, canine and human surfactants. In general, surfactant compositions contain dipalmitoyl-phosphatidylcholine (DPPC) as their phospholipid in an aqueous carrier, either alone or in combination with other phospholipids (United States Patent 5,299,566). Such surfactant compositions may be obtained from natural sources such as the lung or chemically synthesized (United States Patents 4,861,756; 4,826,821 and 4,312,860). In addition, certain proteins associated with surfactant and fragments thereof may be added to phospholipids to enhance their ability to reduce surface tension (United States Patent 5,302,581; 4,659,805). Surfactant-associated proteins may be produced by recombinant DNA technologies (United States Patent 4,912,038; 5,169,761; 4,933,280).

In addition to "SURVANTA" discussed above, several other commercially available surfactants that are suitable for use in accordance with the present invention include, "SURFACTANT TA" (Tokyo Tanabe), and "EXOSURF NEONATAL" (Burroughs Wellcome). "SURFACTANT TA" is a surfactant comprising a mammalian lung extract that contains a phospholipid content of 75-95.5%, a neutral lipid content of

1.8-14%, total cholesterol cont nt of 0-3%, carbohydrate content of 0.1-1.5% and prot in content of 0.5-5% (United States Patent 4,338,301). "EXOSURF NEONATAL" is a protein-free synthetic lung surfactant stored under vacuum as a sterile lyophilized powder. Each 10 ml vial contains 108 mg dipalmitoylphosphatidylcholine, 12 mg cetyl alcohol such as hexadecanol, 8 mg of a non-toxic nonionic surface active agent such as tyloxapol and 47 mg sodium chloride (United States Patent 4,826,821).

Additional suitable compositions include biosynthetic mammalian lung surfactant described in United States Patent 5,387,746, "CUROSURF" described in United States Patent 5,024,995 and "LIQUIVENT". "CUROSURF" is a porcine pulmonary surfactant that contains a polar lipid content of 98.5-99% and a protein content of less than 1.5% (United States Patent 5,024,995). "LIQUIVENT" is an unemulsified neat perfluorooctylbromide-based oxygen carrier/surfactant (United States Patents 5,437,272; 4,987,154).

Furthermore, since the phospholipid content of surfactant in the middle ear system differs from pulmonary surfactant (Coticchia et al., 1991, *Acta Otolaryngol.* 111:1097-1104), surfactant extracted from the middle ear or synthetically produced that mimics its natural composition may also be used for the practice of the present invention.

5.2. ADMINISTRATION OF SURFACTANT

The preferred route of administering surfactant compositions for the practice of the present invention is by inhalation. The treatment continues until an improvement of the eustachian tube dysfunction is observed, e.g., a reduction in opening pressure. Generally, the treated patient is evaluated 10 to 14 days after treatment. While inhalation via the nasal cavity is the preferred method of delivery, surfactants may also be delivered via both nasal and oral cavities. In this connection, surfactant is delivered by a mask which is placed over both the nose and mouth of the individual in need of treatment. Additionally,

devices that are designed for the delivery of pharmaceutical compositions and therapeutic formulations through inhalation via the nasal passage can also be used in this invention.

The surfactant composition, combined with a dispersing agent or dispersant, can be administered in an aerosol formulation as a dry powder or in a solution or suspension with a diluent. As used herein, the term "dispersant" refers to an agent that assists aerosolization of the surfactant. However, since surfactant is itself often used in the art as a dispersant to reduce surface tension caused by atomization of the solution forming a liquid aerosol, an additional dispersant may not be necessary. Amounts of surfactant used vary, being generally within the range of 0.001 and 4% by weight of the formulation. For example, "SURVANTA" may be prepared in the range of 0.001-25 mg/ml, and an optimal dose for administering any surfactant in accordance with the present invention can be readily determined by titration experiments that are well known in the art. Suitable surfactant can be selected on the basis of desired properties, depending on the specific formulation, diluent (in a liquid formulation) or form of powder (in a dry powder formulation), etc.

With either the liquid or dry powder aerosol formulation, the formulation must be aerosolized, i.e., it must be broken down into liquid or solid particles in order to ensure that the aerosolized dose reaches the eustachian tube. In general, the mass median dynamic diameter is 1-10 micrometers in order to ensure that the particles reach the eustachian tube. It is preferred that the particles be in the range of 3-9 micrometers to facilitate entry into the nasopharynx, and minimize entry into the lung (*See* Damms et al., 1995, *Biotechol.* 13:1438-1440). The term "aerosol particle" is used herein to describe the liquid or solid particle suitable for nasal administration, *i.e.*, that will reach the eustachian tube. Other considerations include construction of the delivery device, additional components in the formulation and particle characteristics. These aspects

of administration of a drug are well known in the art, and manipulation of formulations, aerosolization means and construction of a delivery device require only routine experimentation by one of ordinary skill in the art.

With regard to the delivery device, any form of aerosolization known in the art, including but not limited to nebulization, atomization or pump aerosolization of a liquid formulation, and aerosolization of a dry powder formulation, can be used in the practice of the invention. Often, the aerosolization of a liquid or a dry powder formulation requires a propellent. The propellent includes, but is not limited to, halogenated hydrocarbon such as chlorofluorocarbon, a hydrofluorocarbon, a hydrochlorofluorocarbon, or a hydrocarbon such as triflouromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol, and 1,1,1,2-tetrafluoroethane, or combinations thereof.

In a particular aspect of the invention, the device for aerosolization is a metered dose inhaler. A metered dose inhaler provides a specific dosage when administered, rather than a variable dose depending on administration. Such a metered dose inhaler can be used with either a liquid or a dry powder aerosol formulation. Metered dose inhalers are well known in the art. Systems of aerosol delivery, such as the pressurized metered dose inhaler and the dry powder inhaler are disclosed in Newman, S.P., *Aerosol and the Lung*, Clarke, S.W. and Davia, D. editors, pp. 197-22. Alternatively, a jet nebulizer (United States Patent 4,832,012) or an ultrasonic nebulizer (The DeVilbiss Co., Somerset, PA) may be used.

5.2.1. LIQUID AEROSOL FORMULATIONS

The present invention provides liquid aerosol formulations and dosage forms of surfactant for use in treating subjects suffering from eustachian tube dysfunction. In general, such dosage forms contain surfactant composition in a pharmaceutically acceptable diluent. Pharmaceutically acceptable diluents include, but are not limited to, sterile

water, saline, buffered saline, dextrose solution, and the like. In a specific embodiment, a diluent that may be used in the present invention or the pharmaceutical formulation of the present invention is phosphate buffered saline, or a buffered saline solution generally between the pH 7.0-8.0 range, or sterile water.

The liquid aerosol formulation of the present invention may include, as optional ingredients, pharmaceutically acceptable carriers, diluents, solubilizing or emulsifying agents, and excipients.

The liquid aerosol formulations of the present invention will typically be used with a nebulizer. The nebulizer can be either air driven via a compressor or ultrasonically. Any nebulizer known in the art can be used in conjunction with the present invention including, but not limited to, Ultravent, Mallinckrodt, Inc. (St. Louis, MO) and the Acorn II nebulizer (Marquest Medical Products, Englewood, CO). Other nebulizers useful in conjunction with the present invention are described in United States Patents 4,624,251; 3,703,173; 3,561,444; and 4,635,627.

The formulations of the present embodiment may also include other agents useful for stabilization or for the regulation of osmotic pressure. Examples of the agents include, but are not limited to, salts, such as sodium chloride, or potassium chloride, and carbohydrates, such as glucose, galactose or mannose, and the like.

5.2.2. AEROSOL DRY POWDER FORMULATIONS

It is also contemplated that a surfactant composition is used as a dry powder inhaler formulation comprising a finely divided powder form of the surfactant and a dispersant. The form of the surfactant is generally a lyophilized powder. Lyophilized forms of surfactant can be obtained through standard techniques well known in the art.

In another embodiment, the dry powder formulation is composed of a finely divided dry powder containing a surfactant, a dispersing agent and also a bulking agent. Bulking agents useful in conjunction with the present

formulation include such agents as lactos , sorbitol, sucrose or mannitol, in amounts that facilitate th dispersal of the powder from the device.

5.3. EUSTACHIAN TUBE DYSFUNCTION AND ITS ASSOCIATED DISORDERS

The delivery of surfactants by inhalation according to the present invention is used to treat any disorders that are associated with and known to cause eustachian tube dysfunction. These include, but are not limited to, trauma, acute and chronic infection of the upper respiratory tract, acute and chronic allergy or disturbed pressure relationships secondary to mucosal inflammation or congestion. The disorders that benefit from the present invention include, but are not limited to, otologic disorders such as acute OM, chronic OM, OME, barotitis media, acute mastoiditis, acute and chronic otomastoiditis and tympanic membrane atelectasis. These encompass disorders of middle ear ventilation. In addition, surfactants may be administered to an individual to prevent eustachian tube dysfunction, particularly a disorder associated with acute or chronic allergic disease. Furthermore, the present invention is used in situations of eustachian tube dysfunction secondary to acute changes in altitude, e.g., ascent and descent during air flight.

6. EXAMPLE: NEBULIZED SURFACTANT REDUCED EUSTACHIAN TUBE OPENING PRESSURE IN EXPERIMENTALLY-INDUCED OME

6.1. MATERIALS AND METHODS

6.1.1. INDUCTION OF EXPERIMENTAL OME

Streptococcus pneumoniae (ATCC 6305) was subcultured for each experiment in beef heart infusion broth. Stationary phase bacteria were washed and suspended in phosphate-buffered saline to a concentration of 108 colony forming units per milliliter. Aliquots of heat-killed pneumococci were obtained by placing the bacterial suspension in a water bath at 200°C for 45 minutes. Sterility of these aliquots was confirmed with subsequent replating on nutrient agar.

Because of their relatively large tympanic bullae and lack of native middle ear disease, gerbils inoculated with nonviable bacteria hav been th established animal model for OME. The experimental protocol was approved in advance by the Tulane University School of Medicine Advisory Committee for Animal Resources. All experiments were conducted in compliance with the Committee's applicable regulations. Twenty gerbils were anesthetized with ketamine and xylazine via intramuscular injection. Each external auditory canal was cleaned with alcohol. Examination of the canal, the tympanic membrane and the middle ear was accomplished with an operating microscope. 0.1 ml of heat-killed bacterial suspension was introduced into the middle ear space through the tympanic membrane using a 27 gauge spinal needle. After 5 days, the animals were reanesthetized using the same intramuscular injection of ketamine and xylazine. Microscopic evaluation revealed either the presence or absence of effusion. The animals without an effusion in either ear were considered healthy, non-affected subjects, whereas the animals with an effusion in at least one ear were considered affected subjects.

6.1.2. TREATMENT BY NEBULIZED SURFACTANT

Affected animals with effusion in at least one ear, were treated by nebulized surfactant as follows. About 0.5 ml of bovine pulmonary surfactant, "SURVANTA" (Ross Laboratories, Columbus, OH), was suspended in 2 ml of normal saline and placed in a nebulizer (Baxter Healthcare Corp., Valencia, CA). Affected gerbils were housed in a ventilated chamber to which the nebulizer was attached (Figure 2). The nebulizer was activated by room air delivered at low flow delivering the total volume of 2.5 ml over a period of 4-5 minutes. Each affected animal received 2.5 ml nebulized surfactant three times per day for 5 days. They were then sacrificed for examination.

6.1.3. MEASUREMENT OF EUSTACHIAN TUBE OPENING PRESSURE

Eustachian tube opening pressure was measured as follows. Immediately following sacrifice of each animal, their tympanic bulla were surgically exposed and cannulated with a 21 gauge butterfly needle. This needle was fixed in place with Krazy Glue (Borden, Inc., Columbus, OH). The external ear canals were filled with epoxy glue (Loctite Corp., Cleveland, OH). Epoxy was also placed over the cannulation site at the tympanic bullae to ensure an airtight system for pressure measurement. The butterfly needle was connected to a closed circuit consisting of a pressure transducer, a stopcock and a syringe attached to a infusion pump and a monitor. Air was slowly introduced into the tympanic bullae at a rate of 5 ml/minute providing steady pressurization of the system. This pressurization was monitored until an abrupt loss of pressure in the system was noted indicative of eustachian tube opening and release of pressure into the nasopharynx. The pressure at which this occurred was defined as the eustachian tube opening pressure. With each measurement, the system was opened to atmospheric pressure allowing the eustachian tube to close. This procedure was repeated for a total of five cycles and the mean value for the set was calculated and recorded.

6.2. RESULTS

In 20 animals, 27 ears developed effusions following inoculation with *S. pneumoniae* (67.5%). Two animals died during post-inoculation examination, one with bilateral effusions and the other with one ear affected. Eustachian tube opening pressure was measured in 30 of 36 ears (83.3%). Figure 3 depicts a sample tracing obtained during the tubal opening studies. Tympanic membrane perforations precluded accurate measurement of opening pressure in 6 ears. Mean opening pressure in ears without effusion (n=10, healthy ears) was 42.8 mmHg. Mean opening pressure in the ears with effusion that had undergone treatment with nebulized surfactant (n=20) was 41.4 mmHg, as depicted in Figure 4. The

differ nce between these two valu s was not statistically significant ($t = 0.32$; $p > 0.50$). Therefore, surfactant treatment of affected animals by nebulization reduced the opening pressure of eustachian tube to a level similar to the ears of normal, unaffected animals. This result indicates that delivery of a surface active substance such as surfactant by inhalation is a clinically practical, non-invasive and efficacious treatment for eustachian tube dysfunction.

The present invention is not to be limited in scope by the exemplified embodiments, which are intended as illustrations of individual aspects of the invention. Indeed, various modifications for the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

All publications cited herein are incorporated by reference in their entirety.

WHAT IS CLAIMED IS:

1. A method for treating eustachian tube dysfunction which results in a disorder of middle ear ventilation in an individual in need of such treatment, comprising administering an effective amount of a surfactant by inhalation to reduce eustachian tube opening pressure.

2. The method of Claim 1 in which the surfactant is mammalian surfactant.

3. The method of Claim 2 in which the mammalian surfactant is bovine, porcine, canine or human surfactant.

4. The method of Claim 1 in which the surfactant is pulmonary surfactant.

5. The method of Claim 1 in which the surfactant is synthetically produced.

6. The method of Claim 1 in which the eustachian tube dysfunction is associated with acute or chronic otitis media.

7. The method of Claim 1 in which the eustachian tube dysfunction is associated with otitis media with effusion.

8. The method of Claim 1 in which the eustachian tube dysfunction is associated with acute changes in altitude.

9. The method of Claim 1 in which the eustachian tube dysfunction is associated with acute or chronic allergic disease.

10. The method of Claim 1 in which the eustachian dysfunction is associated with acute or chronic infectious disease of the upper respiratory tract.

11. The method of Claim 1 in which the surfactant comprises a bovine lung extract that contains 25 mg/ml phospholipids which includes 11.0-15.5 mg/ml disaturated phosphatidylcholine, 0.5-1.75 mg/ml triglycerides, 1.4-3.5 mg/ml free fatty acids, and less than 1.0 mg/ml SP-B and SP-C proteins.

12. The method of Claim 1 in which the surfactant comprises a mammalian lung extract that contains a phospholipid content of 75-95.5%, a neutral lipid content of 1.8-14%, total cholesterol content of 0-3%, carbohydrate content of 0.1-1.5% and protein content of 0.5-5%.

13. The method of Claim 1 in which the surfactant comprises a protein-free synthetic lung surfactant that contains 10.8 mg/ml dipalmitoylphosphatidylcholine, 1.2 mg/ml hexadecanol, 0.8 mg/ml tyloxapol and 4.7 mg/ml sodium chloride.

14. The method of Claim 1 in which the surfactant comprises a porcine pulmonary surfactant that contains a polar lipid content of 98.5-99% and a protein content of less than 1.5%.

15. The method of Claim 1 in which the inhalation is by nebulization.

16. The method of Claim 1 in which the surfactant is in a liquid aerosol.

17. The method of Claim 1 in which the surfactant is in a dry powder.

18. A pharmaceutical composition for treating eustachian tube dysfunction by inhalation, comprising an effective amount of a surfactant as an active therapeutic agent and a propellant.

19. The pharmaceutical composition of Claim 18 in which the surfactant and propellant are formulated to generate an aerosol particle having a mass median dynamic diameter between 3-9 micrometers.

20. The pharmaceutical composition of Claim 18 in which the surfactant and propellant are in the form of a nasal spray.

21. The pharmaceutical composition of Claim 18 in which the surfactant and propellant are delivered in a mask.

22. The pharmaceutical composition of Claim 18 in which the surfactant comprises a bovine lung extract that contains 25 mg/ml phospholipids which includes 11.0-15.5 mg/ml disaturated phosphatidylcholine, 0.5-1.75 mg/ml triglycerides, 1.4-3.5 mg/ml free fatty acids, and less than 1.0 mg/ml SP-B and SP-C proteins.

23. The pharmaceutical composition of Claim 18 in which the surfactant comprises a protein-free synthetic lung surfactant that contains 10.8 mg/ml dipalmitoylphosphatidylcholine, 1.2 mg/ml hexadecanol, 0.8 mg/ml tyloxapol and 4.7 mg/ml sodium chloride.

24. The pharmaceutical composition of Claim 18 in which the surfactant comprises 108 mg dipalmitoylphosphatidylcholine, 12 mg cetyl alcohol such as hexadecanol, 8 mg of a non-toxic nonionic surface active agent such as tyloxapol and 47 mg sodium chloride.

25. The pharmaceutical composition of Claim 18 in which the surfactant comprises a porcine pulmonary surfactant that contains a polar lipid cont nt of 98.5-99% and a protein content of less than 1.5%.

26. A method for preventing eustachian tube dysfunction in an individual, comprising administering an effective amount of a surfactant by inhalation to maintain eustachian tube opening pressure.

27. The method of Claim 26 in which the surfactant is mammalian surfactant.

28. The method of Claim 27 in which the mammalian surfactant is bovine, porcine, canine or human surfactant.

29. The method of Claim 26 in which the surfactant is pulmonary surfactant.

30. The method of Claim 26 in which the surfactant is synthetically produced.

31. The method of Claim 26 in which the eustachian tube dysfunction is associated with acute or chronic otitis media.

32. The method of Claim 26 in which the eustachian tube dysfunction is associated with otitis media with effusion.

33. The method of Claim 26 in which the eustachian tube dysfunction is associated with acute changes in altitude.

34. The method of Claim 26 in which the eustachian tube dysfunction is associated with acute or chronic allergic disease.

35. The method of Claim 26 in which the eustachian tube dysfunction is associated with acute or chronic infectious disease of the upper respiratory tract.

36. The method of Claim 26 in which the surfactant comprises a bovine lung extract that contains 25 mg/ml phospholipids which includes 11.0-15.5 mg/ml disaturated phosphatidylcholine, 0.5-1.75 mg/ml triglycerides, 1.4-3.5 mg/ml free fatty acids, and less than 1.0 mg/ml SP-B and SP-C proteins.

37. The method of Claim 26 in which the surfactant comprises a mammalian lung extract that contains a phospholipid content of 75-95.5%, a neutral lipid content of 1.8-14%, total cholesterol content of 0-3%, carbohydrate content of 0.1-1.5% and protein content of 0.5-5%.

38. The method of Claim 26 in which the surfactant comprises a protein-free synthetic lung surfactant that contains 10.8 mg/ml dipalmitoylphosphatidylcholine, 1.2 mg/ml hexadecanol, 0.8 mg/ml tyloxapol and 4.7 mg/ml sodium chloride.

39. The method of Claim 26 in which the surfactant comprises a porcine pulmonary surfactant that contains a polar lipid content of 98.5-99% and a protein content of less than 1.5%.

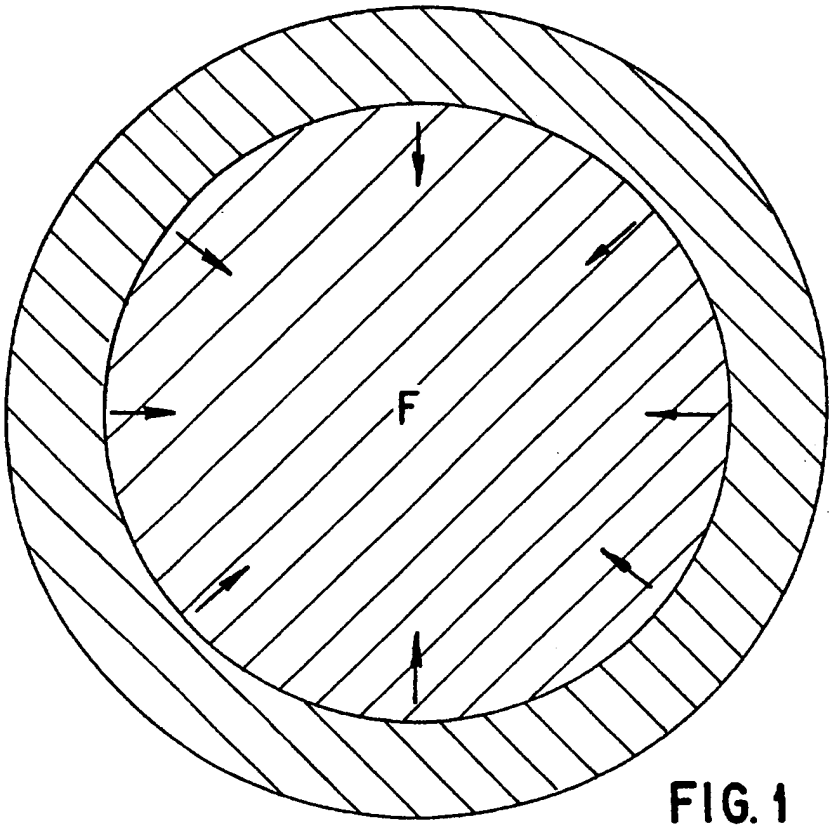


FIG. 1

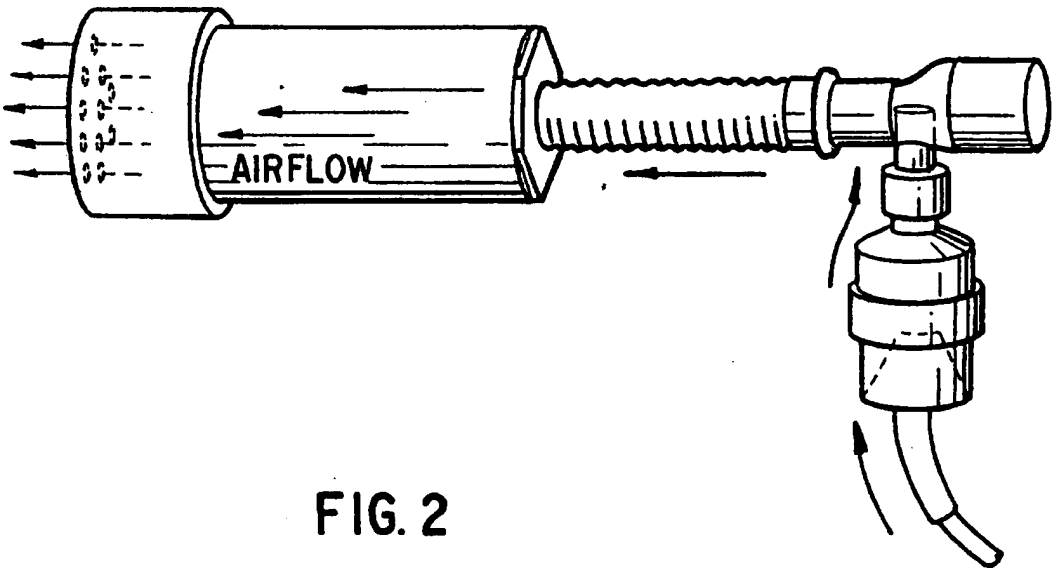


FIG. 2

FIG. 3

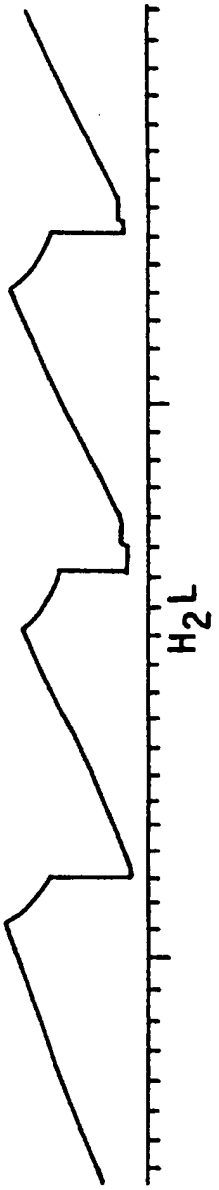
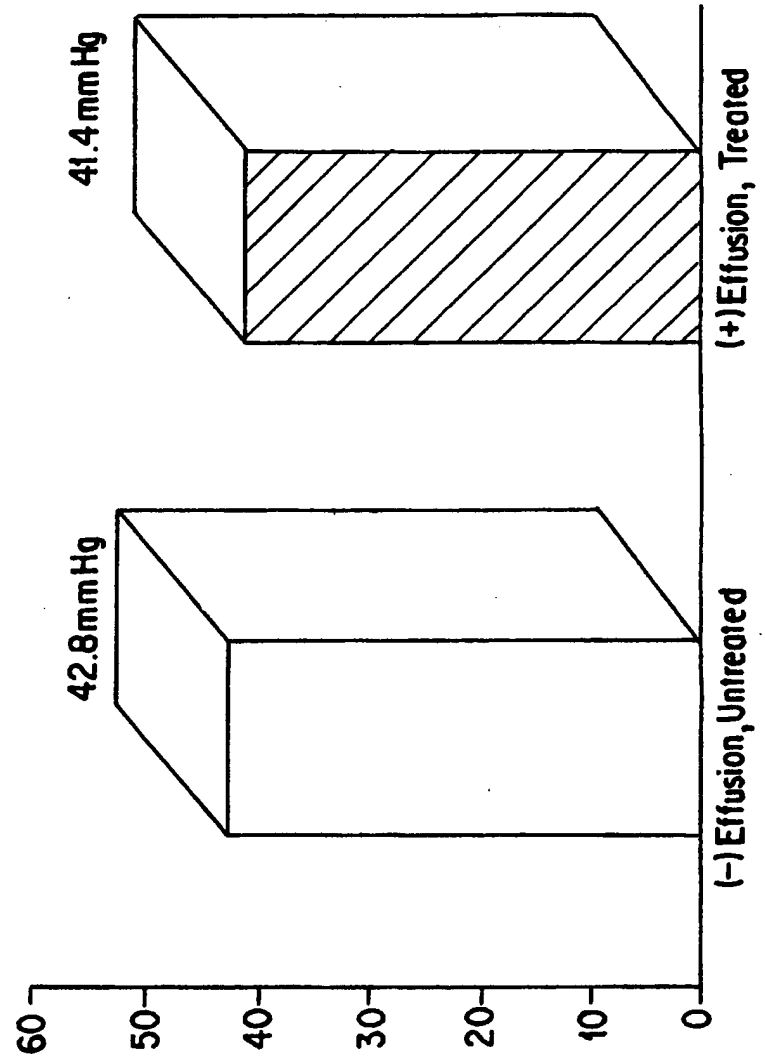

H_2L

FIG. 4


41.4mmHg
42.8mmHg
(+)Effusion, Treated
(-) Effusion, Untreated
60
50
40
30
20
10
0

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/02294

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/12, 9/14, 9/72, 38/03
US CL :514/12; 424/45, 46, 489, 502
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/12; 424/45, 46, 489, 502

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, EMBASE, MEDLINE, BIOSIS, SCISEARCH, CAPLUS
search terms: eustachian tube, surfactant, otitis

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PETER et al. Surfactant and isoprenaline effect on eustachian tube opening in rats with acute otitis media. American Journal of Otolaryngology. 1990, Vol. 11, No. 6, pages 389-392, see entire document.	1-10, 26-35
Y	WHITE, P. Effect of exogenous surfactant on eustachian tube function in the rat. American Journal of Otolaryngology. September 1989, Vol. 10. No. 5. pages 301-304, see entire document.	1-10, 26-35
Y	FORNADLEY et al. The effect of surfactant on eustachian tube function in gerbil model or otitis media with effusion. Otolaryngology-Head and Neck Surgery. 1994, Vol. 110, No. 1, pages 110-114, see entire document.	1-4, 7, 26-29, 32

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 05 JUNE 1996	Date of mailing of the international search report 01 JUL 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ANISH GUPTA Telephone No. (703) 308-0196

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/02294

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,306,483 A (A.J. MAUTONE) 26 April 1994 (26/04/94), see entire document.	1, 12, 16, 18-20, 37
Y	US 5,299,566 A (C.W. DAVIS ET AL.) 05 April 1994 (05/04/94), see column 5 and column 6, lines 15-39.	1, 13, 15, 23, 24, 38
Y	US 5,024,995 A (B. ROBERTSON ET AL.) 18 June 1991 (18/06/91), see entire document.	1, 4, 14, 25, 29, 39
Y	US 4,826,821 A (J.A. CLEMENTS) 02 May 1989 (02/05/89), see entire document.	1, 5, 13, 17, 23, 24, 30, 38
Y	US 5,302,581 A (V.K. SARIN ET AL.) 12 April 1994 (12/04/94), see entire document, especially column 9, lines 55-68.	1, 11, 22, 36
A, E	US 5,407,914 A (C.G. COCHRANE ET AL.) 18 April 1995 (18/04/95), see entire document, especially column 15.	1, 4, 11, 22, 29, 36
A	US 5,013,720 A (J.A. WHITSETT) 07 May 1991 (07/05/91), see entire document.	1, 4, 11, 22, 36